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## Clinical outcomes in patients with atrial fibrillation receiving amiodarone on NOACs vs. warfarin

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# Background

- Amiodarone is a potent inhibitor of the CYP450:3A4 and inhibitor of the P-glycoprotein, both of which metabolize new oral anticoagulants (NOACs).
- Patients who are on NOACs and are concomitantly treated with amiodarone may have a higher risk of major bleeding according to recent retrospective trials.
- Whether this increased risk outweighs the benefits of NOACs compared to warfarin is unknown.

# Aim of the study

- To compare clinical outcomes between NOACs and warfarin in patients with atrial fibrillation (AF) being treated with amiodarone.

# Methods

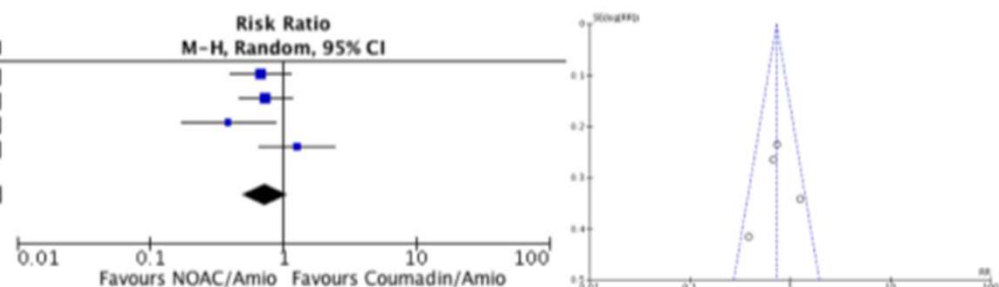
- A systematic review of MEDLINE, Cochrane, and Embase for randomized controlled trials that compared NOACs to warfarin for prophylaxis of ischemic stroke/thromboembolic events (TEs) in patients with AF and reported outcomes on TE, major bleeding, and intracranial bleeding(ICB).

# Results

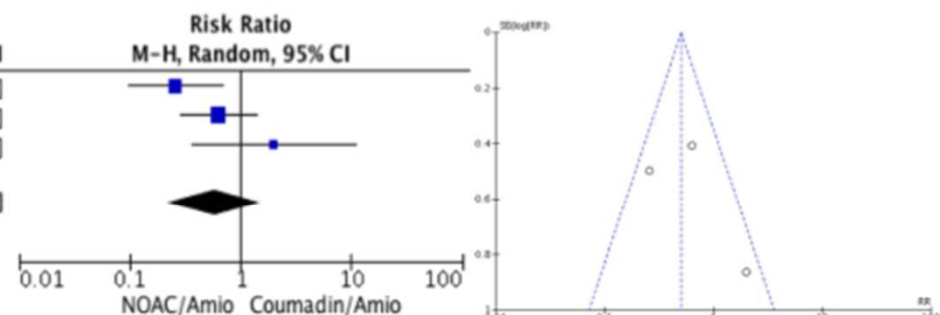
- The total number of patients on amiodarone was 6197.
- There was no statistical difference for TE prevention (RR, 0.73; 95% CI 0.50–1.07), major bleeding (RR, 1.02; 95% CI 0.68–1.53), and ICB (RR, 0.58; 95% CI 0.22–1.51) between patients on NOACs when compared to patients on warfarin in patients with AF being treated with amiodarone.

**(a) Stroke**

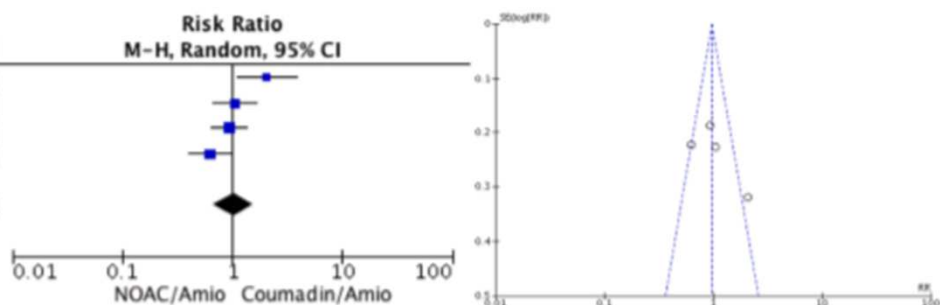
Study or Subgroup	NOAC/Amio		Coumadin/Amio		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
ARISTOTLE 2011	23	1009	35	1042	29.1%	0.68 [0.40, 1.14]
ENGAGE AF 2013	31	866	40	827	32.9%	0.74 [0.47, 1.17]
RE-LY, 2009	8	665	20	644	16.4%	0.39 [0.17, 0.87]
ROCKET-AF 2011	19	572	15	572	21.6%	1.27 [0.65, 2.47]
<b>Total (95% CI)</b>		<b>3112</b>		<b>3085</b>	<b>100.0%</b>	<b>0.73 [0.50, 1.07]</b>
Total events	81		110			
Heterogeneity: Tau <sup>2</sup> = 0.06; Chi <sup>2</sup> = 5.04, df = 3 (P = 0.17); I <sup>2</sup> = 40%						
Test for overall effect: Z = 1.62 (P = 0.11)						

**(b) Intracranial Bleeding**

Study or Subgroup	NOAC/Amio		Coumadin/Amio		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
ARISTOTLE 2011	5	1009	20	1042	36.8%	0.26 [0.10, 0.69]
ENGAGE AF 2013	10	866	15	827	42.3%	0.64 [0.29, 1.41]
ROCKET-AF 2011	4	572	2	572	20.9%	2.00 [0.37, 10.88]
<b>Total (95% CI)</b>		<b>2447</b>		<b>2441</b>	<b>100.0%</b>	<b>0.58 [0.22, 1.51]</b>
Total events	19		37			
Heterogeneity: Tau <sup>2</sup> = 0.40; Chi <sup>2</sup> = 4.67, df = 2 (P = 0.10); I <sup>2</sup> = 57%						
Test for overall effect: Z = 1.11 (P = 0.26)						

**(c) Major Bleeding**

Study or Subgroup	NOAC/Amio		Coumadin/Amio		Weight	Risk Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
ROCKET-AF 2011	29	572	14	572	19.8%	2.07 [1.11, 3.88]
RE-LY, 2009	38	665	35	644	25.7%	1.05 [0.67, 1.64]
ENGAGE AF 2013	53	866	54	827	28.5%	0.94 [0.65, 1.35]
ARISTOTLE 2011	31	1009	51	1042	26.0%	0.63 [0.41, 0.97]
<b>Total (95% CI)</b>		<b>3112</b>		<b>3085</b>	<b>100.0%</b>	<b>1.02 [0.68, 1.53]</b>
Total events	151		154			
Heterogeneity: Tau <sup>2</sup> = 0.12; Chi <sup>2</sup> = 9.57, df = 3 (P = 0.02); I <sup>2</sup> = 69%						
Test for overall effect: Z = 0.08 (P = 0.93)						



**Fig. 4** Forrest plots and funnel plots for the comparative analyses of clinical outcomes in patients concomitantly using NOAC and amiodarone vs Coumadin and amiodarone. **a** Stroke. **b** Major bleeding, **c** Intracranial bleeding

# Conclusions

- The concomitant use of amiodarone and NOACs in patients with NVAF appears to be safe and effective as compared with warfarin, as it does not negatively impact clinical outcomes such as TE, major bleeding, and ICB.
- However, physicians should consider alternative antiarrhythmic drugs in patients with NVAF and without structural heart disease (as suggested by guidelines), in order to avoid unnecessary drug interactions.